4164-01-P

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

[Docket No. FDA-2020-N-1245]

Drug Products Approved in Abbreviated New Drug Applications Before the Enactment of the Hatch-Waxman Amendments; Establishment of a Public Docket; Request for Comments

AGENCY: Food and Drug Administration, Health and Human Services (HHS).

ACTION: Notice; establishment of a public docket; request for comments.

SUMMARY: The Food and Drug Administration (FDA or Agency) is announcing the establishment of a public docket to solicit comments on several issues related to FDA's post-approval regulation of certain drug products approved in abbreviated applications before the Drug Price Competition and Patent Term Restoration Act of 1984 (Hatch-Waxman Amendments) amended the Federal Food, Drug, and Cosmetic Act (FD&C Act) to establish the current abbreviated new drug application (ANDA) process. Because these pre-Hatch-Waxman abbreviated new drug applications (referred to in this notice as "PANDAs") were submitted and approved under the provisions of the FD&C Act that apply to 505(b) new drug applications, they can serve as a reference listed drug (RLD) for ANDAs and can also be a listed drug relied on by 505(b)(2) applications. PANDAs have historically been overseen by FDA's Office of Generic Drugs, and FDA is aware that there may be some confusion about the applicability of certain statutory and regulatory provisions to PANDAs. FDA is seeking input from holders of PANDAs and other interested persons regarding whether there are regulatory or policy rationales for treating PANDAs differently from other 505(b) applications in certain respects.

DATES: Submit either electronic or written comments by [INSERT DATE 120 DAYS AFTER DATE OF PUBLICATION IN THE *FEDERAL REGISTER*].

ADDRESSES: FDA is establishing a docket for public comments on this document. The docket number is FDA-2020-N-1245. The docket will close on [INSERT DATE 120 DAYS AFTER DATE OF PUBLICATION IN THE *FEDERAL REGISTER*]. Submit either electronic or written comments by that date. Please note that late, untimely filed comments will not be considered. Electronic comments must be submitted on or before [INSERT DATE 120 DAYS AFTER DATE OF PUBLICATION IN THE *FEDERAL REGISTER*]. The https://www.regulations.gov electronic filing system will accept comments until 11:59 p.m. Eastern Time at the end of [INSERT DATE 120 DAYS AFTER DATE OF PUBLICATION IN THE *FEDERAL REGISTER*]. Comments received by mail/hand delivery/courier (for written/paper submissions) will be considered timely if they are postmarked or the delivery service acceptance receipt is on or before that date.

You may submit comments as follows:

Electronic Submissions

Submit electronic comments in the following way:

- Federal eRulemaking Portal: https://www.regulations.gov. Follow the instructions for submitting comments. Comments submitted electronically, including attachments, to https://www.regulations.gov will be posted to the docket unchanged. Because your comment will be made public, you are solely responsible for ensuring that your comment does not include any confidential information that you or a third party may not wish to be posted, such as medical information, your or anyone else's Social Security number, or confidential business information, such as a manufacturing process. Please note that if you include your name, contact information, or other information that identifies you in the body of your comments, that information will be posted on https://www.regulations.gov.

- If you want to submit a comment with confidential information that you do not wish to be made available to the public, submit the comment as a written/paper submission and in the manner detailed (see "Written/Paper Submissions" and "Instructions").

Written/Paper Submissions

Submit written/paper submissions as follows:

- Mail/Hand delivery/Courier (for written/paper submissions): Dockets Management Staff (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852.
- For written/paper comments submitted to the Dockets Management Staff, FDA will post your comment, as well as any attachments, except for information submitted, marked and identified, as confidential, if submitted as detailed in "Instructions."

Instructions: All submissions received must include the Docket No. FDA-2020-N-1245 for "Drug Products Approved in Abbreviated New Drug Applications Before the Enactment of the Hatch-Waxman Amendments; Establishment of a Public Docket; Request for Comments." Received comments, those filed in a timely manner (see ADDRESSES), will be placed in the docket and, except for those submitted as "Confidential Submissions," publicly viewable at https://www.regulations.gov or at the Dockets Management Staff between 9 a.m. and 4 p.m., Monday through Friday, 240-402-7500.

- Confidential Submissions--To submit a comment with confidential information that you do not wish to be made publicly available, submit your comments only as a written/paper submission. You should submit two copies total. One copy will include the information you claim to be confidential with a heading or cover note that states "THIS DOCUMENT CONTAINS CONFIDENTIAL INFORMATION." The Agency will review this copy, including the claimed confidential information, in its consideration of comments. The second copy, which will have the claimed confidential information redacted/blacked out, will be available for public viewing and posted on https://www.regulations.gov. Submit

both copies to the Dockets Management Staff. If you do not wish your name and contact information to be made publicly available, you can provide this information on the cover sheet and not in the body of your comments and you must identify this information as "confidential." Any information marked as "confidential" will not be disclosed except in accordance with 21 CFR 10.20 and other applicable disclosure law. For more information about FDA's posting of comments to public dockets, see 80 FR 56469, September 18, 2015, or access the information at: https://www.govinfo.gov/content/pkg/FR-2015-09-18/pdf/2015-23389.pdf.

Docket: For access to the docket to read background documents or the electronic and written/paper comments received, go to https://www.regulations.gov and insert the docket number, found in brackets in the heading of this document, into the "Search" box and follow the prompts and/or go to the Dockets Management Staff, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852, 240-402-7500.

FOR FURTHER INFORMATION CONTACT: Melissa Mannion, Center for Drug Evaluation and Research, Food and Drug Administration, 10903 New Hampshire Ave., Bldg. 75 Room 1611, Silver Spring, MD 20993, 301-796-2747, Melissa.Mannion@fda.hhs.gov.

SUPPLEMENTARY INFORMATION:

I. Background

A. Abbreviated New Drug Applications Before the Hatch-Waxman Amendments

After the enactment of the FD&C Act (Pub. L. 75-717) in 1938, new drug products were required to be approved on the basis of safety before they could be marketed. Between 1938 and 1962, if a drug product obtained approval, FDA considered drug products that were identical, related, or similar to the approved product to be covered by that approval; such identical, related, or similar products were marketed without independent approval. An identical, related, or similar drug includes another brand, potency, dosage form, salt, or ester of the same drug moiety related in chemical structure or known pharmacological properties (see 21 CFR 310.6(b)(1)). In

1962, the Kefauver-Harris Drug Amendments (Pub. L. 87-781) amended the FD&C Act to require that new drug products also be shown to be effective in order to obtain approval of a new drug application (NDA). After the enactment of the Kefauver-Harris Drug Amendments, FDA initiated the Drug Efficacy Study Implementation (DESI) to evaluate the effectiveness of drug products that had been approved between 1938 and 1962 solely on the basis of safety. DESI also covered the identical, related, or similar products that had entered the market without approval. If drug products were determined to be effective for one or more indications,[1] manufacturers that were already marketing under an NDA were required to submit a supplement to update the application and revise the product labeling as necessary. Manufacturers of drug products that were identical, related, or similar were required to submit applications for their drug products.

FDA introduced the concept of an "abbreviated new drug application" in 1968[2] as a vehicle for approval of certain drugs affected by the DESI review, and in 1970, FDA published a final rule establishing a regulatory pathway for submission of abbreviated applications for these drugs (see 35 FR 6574 (April 24, 1970); see also 34 FR 2673 (February 27, 1969)). This abbreviated approval mechanism was created to offer manufacturers of certain drugs a streamlined and more administratively efficient path to seek FDA approval as part of the DESI review (47 FR 46622 at 46631 to 46632 (October 19, 1982)).

When a drug product subject to the DESI review was determined to be effective for one or more indications, FDA would issue a *Federal Register* notice (DESI notice) for that drug product describing the DESI review findings and stating whether abbreviated new drug

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[1] If a drug product was found to be less than effective for one or more labeled indications in FDA's initial DESI review, the Agency provided an opportunity to submit additional data and eventually an opportunity for a hearing on those indications found to be less than effective. FDA considered the basis of any hearing request and either granted or denied the hearing request and published its final determination in the *Federal Register*. If FDA's final determination classified a drug product as effective for an indication, those marketing that drug product and drugs identical, related or similar to it were required to obtain approved applications for continued marketing for that indication. If FDA's final determination classified the drug product as lacking substantial evidence of effectiveness for an indication, the product and those identical, related or similar to it could no longer be legally marketed for that indication.

[2] See the Washington briefing on FDA's drug efficacy review, FDA Papers, at pp. 10-12 (March 1968) and Address of Commissioner James L. Goddard, M.D., at the Alpha Omega Alpha Lecture at Yale New Haven Medical Center on New Drug Research and Development (April 17, 1968).

applications that met specified criteria could be submitted to FDA (see generally 35 FR 11273 (July 14, 1970); 35 FR 6574) for products that had not been marketed under an NDA. Such a finding allowed manufacturers to submit an abbreviated new drug application (i.e., a PANDA) in lieu of an NDA.

For approval of PANDAs, FDA relied on the evidence of effectiveness that had been provided, reviewed, and accepted during the DESI process. FDA evaluated the safety of these drug products on the basis of information included in NDAs submitted prior to 1962, as well as the subsequent marketing experience with the drugs (see 54 FR 28872 at 28873 (July 10, 1989)). PANDAs were submitted under section 505(b) of the FD&C Act and approved under section 505(c) of the FD&C Act.[3]

Because the history of FDA review of applications for antibiotic drug products is more complex and historically many were subject to section 507 of the FD&C Act (21 U.S.C. 357 (1994 ed.); repealed upon the enactment of the Food and Drug Administration Modernization Act of 1997 (Pub. L. 105-115)), the scope of this notice is limited to drug products approved in PANDAs under section 505 of the FD&C Act prior to the Hatch-Waxman Amendments; this notice does not cover applications for antibiotic drug products that were originally submitted under section 507 of the FD&C Act.[4]

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[3] The content of section 505(b) of the FD&C Act regarding the required contents of an application remained largely unchanged following the enactment of the Hatch-Waxman Amendments, except for changes related to new patent submission requirements and, for applications submitted pursuant to section 505(b)(2) of the FD&C Act, patent certification requirements.

[4] Prior to the enactment of the Food and Drug Administration Modernization Act of 1997, applications for antibiotic drugs were generally approved for safety and effectiveness under section 507 of the FD&C Act rather than under section 505 of the FD&C Act. For purposes of section 507, the term "*antibiotic drug*" was defined as any drug intended for use by man containing any quantity of any chemical substance which is produced by a microorganism and which has the capacity to inhibit or destroy microorganisms in dilute solution (including the chemically synthesized equivalent of any such substance). See 21 U.S.C. 357 (1964 ed.; 1994 ed.). Although there was a mechanism for approving abbreviated applications for antibiotics under section 507 that pre-dated the Hatch-Waxman Amendments, in this notice the term *PANDAs* refers only to those applications submitted under section 505(b) of the FD&C Act, and not to applications for antibiotic drug products submitted under section 507 of the FD&C Act. FDA intends to address these antibiotic products separately.

Because PANDAs could be for products that were "similar or related" to, and not just "duplicates"[5] of, drug products approved in NDAs before October 10, 1962, and listed in DESI notices (pre-1962 NDA drug products), FDA's "Approved Drug Products With Therapeutic Equivalence Evaluations" (Orange Book) lists both unique products approved in PANDAs (i.e., no NDA was ever approved for the identical drug product), and products approved in PANDAs that may be duplicates of pre-1962 NDA drug products. In the Orange Book, a product approved in a PANDA typically is identified as an "ANDA." (The application type for a product is identified in the Orange Book by either an "*N*" (for an NDA) or an "*A*" (for an ANDA) before the application number.)

Although the regulations establishing the pathway for PANDAs were similar in some respects to the ANDA pathway created by the Hatch-Waxman Amendments and described in section 505(j) of the FD&C Act, the requirements under the old regulatory pathway (which evolved over the decade-plus in which it was operational before the Hatch-Waxman Amendments) also differed in many respects from current ANDA requirements. For example, although the conditions of use and labeling for PANDA products had to be in accord with the relevant DESI notice (which frequently covered a class of drugs that included multiple products and multiple active ingredients) (see, e.g., 36 FR 11227 (June 10, 1971); 35 FR 18215 (November 28, 1970); and 35 FR 12356 (August 1, 1970)), PANDA products were not required to have the same labeling as a particular pre-1962 NDA drug product listed in the DESI notice. In addition, although PANDAs were required to include adequate data to assure biological availability of the drug if the relevant DESI notice for that drug specified that such data should be submitted for the formulation intended for marketing, PANDAs generally did not have to include data to demonstrate bioequivalence to a particular pre-1962 NDA drug product (see, e.g., 21 CFR 130.4(f)(3) (1971 ed.) and 21 CFR 314.2(f)(3) (1984 ed.)). In addition, drug products

[5] In the context of PANDAs, the term '*duplicate*' applied to a drug product that was the same as an already approved drug product in dosage form, route of administration, kind and amount of active ingredient, indication(s), and any other conditions of use. See 54 FR 28872 at 28872 (July 10, 1989).

with a different formulation, active ingredient, route of administration, dosage form, or strength than the pre-1962 NDA drug products listed in the DESI notice could be submitted in PANDAs. Prior to the Hatch-Waxman Amendments, there were also no requirements related to patent listing or patent certification or exclusivity for PANDAs or other applications approved under section 505(c) of the FD&C Act.

B. Hatch-Waxman Amendments

In 1984, the Hatch-Waxman Amendments added section 505(b)(2) and section 505(j) to the FD&C Act. These sections provide an abbreviated approval pathway for submission of two types of applications: section 505(b)(2) new drug applications (505(b)(2) applications) and section 505(j) abbreviated new drug applications (for purposes of this notice, referred to hereinafter as "505(j) ANDAs"). A 505(b)(2) application is an NDA submitted under section 505(b)(1) and approved under section 505(c) of the FD&C Act that contains full reports of investigations of safety and effectiveness, where at least some of the information required for approval comes from studies not conducted by or for the applicant and for which the applicant has not obtained a right of reference or use (e.g., the Agency's finding of safety and/or effectiveness for a listed drug). A 505(j) ANDA is an application that requests FDA approval to market a duplicate of a listed drug.[6] Regulations implementing the Hatch-Waxman Amendments define a *listed drug* as a new drug product that has been approved under section 505(c) of the FD&C Act for safety and effectiveness or under section 505(j) of the FD&C Act, which has not been withdrawn or suspended under section 505(e)(1) through (5) or section 505(j)(6) of the FD&C Act, and which has not been withdrawn from sale for what FDA has determined are reasons of safety or effectiveness. Listed drug status is evidenced by the drug product's identification in the current edition of FDA's "Approved Drug Products With Therapeutic Equivalence Evaluations" (the list) as an approved drug. A drug product is deemed to be a listed

[6] In the context of the Hatch-Waxman Amendments, the term *duplicate* generally refers to a "drug product that has the same active ingredient(s), dosage form, strength, route of administration, and conditions of use as a listed drug…" 54 FR 28872 at 28877.

drug on the date of approval for the NDA or ANDA for that drug product. (See § 314.3(b) (21 CFR 314.3(b)), as amended at 81 FR 69580 at 69638 (October 6, 2016); see also section 505(j)(2)(A), (j)(7) of the FD&C Act).

FDA regulations require an applicant to refer in its 505(j) ANDA to the specific listed drug on which the applicant relies in seeking approval of the 505(j) ANDA (§ 314.94(a)(3) (21 CFR 314.94(a)(3)); see also section 505(j)(2) of the FD&C Act). The listed drug that a generic applicant seeks to duplicate is commonly referred to as the *reference listed drug* (RLD) (see definition in § 314.3(b)). A 505(j) ANDA applicant must show, among other things, that the proposed generic drug is bioequivalent to the RLD, and that it has the same active ingredient(s), conditions of use, route of administration, dosage form, strength, and (with limited exceptions) labeling as the RLD (section 505(j)(2)(A), (j)(2)(C), and (j)(4) of the FD&C Act; see also § 314.94(a)). We note that certain differences between an RLD and a proposed generic drug product may be permitted in an ANDA if these differences are the subject of an approved suitability petition (see section 505(j)(2)(C) of the FD&C Act and 21 CFR 314.93). An applicant may submit a suitability petition to FDA requesting permission to submit an ANDA for a generic drug product that differs from an RLD in its route of administration, dosage form, or strength or that has one different active ingredient in a fixed-combination drug product (ibid.).

Because a 505(j) ANDA applicant is relying on FDA's finding that the RLD is safe and effective, FDA's general practice is to designate as RLDs drug products that have been approved under section 505(c) for safety and effectiveness. Similarly, FDA regulations require a 505(b)(2) applicant to identify in its application each listed drug for which FDA has made a finding of safety and effectiveness on which the applicant relies in seeking approval of its proposed drug product (21 CFR 314.54(a)(1)(iii)).

Listed drugs appear in the Orange Book, and beginning in 1992, the Orange Book also began identifying which listed drugs were designated as RLDs to aid 505(j) ANDA applicants. The listed drugs that were designated as RLDs were labeled with a "+" sign in the paper version

of the Orange Book, and with the word "Yes" in the column titled RLD in the electronic version of the Orange Book. Before 2017, the "+" sign and the word "Yes" in the column labeled RLD were used to denote at times an RLD and at other times a reference standard, which is the drug product selected by FDA that an applicant seeking approval of a 505(j) ANDA must use in conducting an in vivo bioequivalence study required for approval of the ANDA (§ 314.3(b)).

The reference standard selected by FDA is ordinarily the RLD. However, at times the reference standard is a drug product other than the RLD. For example, if the NDA RLD is no longer marketed, FDA generally will select as the reference standard a previously approved 505(j) ANDA that refers to that RLD. Where the RLD was no longer marketed and FDA selected a new reference standard, FDA's practice prior to 2017 was to identify the reference standard with the "+" sign in the paper version of the Orange Book and "Yes" in the RLD column of the electronic version of the Orange Book; FDA also would move the previously identified RLD to the discontinued section of the Orange Book without a "+" sign in the paper version or RLD designation in the electronic version of the Orange Book.

Because the "+" sign or RLD designation in some cases identified drug products that were RLDs as well as reference standards, and in other cases identified reference standards that were not also the RLD, there may have been some confusion among 505(j) ANDA applicants about which product to cite as the RLD when the reference standard and RLD were not the same drug product. Inconsistent use of terminology, as well as certain long-standing FDA practices, may have added to this confusion.

C. FDA's Current Identification of RLDs and Reference Standards in the Orange Book

In 2017, FDA began to separately identify in the Orange Book which listed drugs, including some in the "Discontinued Drug Product List" (discontinued section), are designated as RLDs, and which listed drugs in the Active Section (i.e., in the sections entitled "Prescription Drug Product List" and "Over-the-Counter Drug Product List") are selected as reference standards. In the electronic version of the Orange Book, there is one column that identifies

RLDs and a separate column that identifies reference standards. In the printed version of the Orange Book, the RLDs and reference standards are identified by distinct symbols.

These changes to the Orange Book were intended to provide clarity to 505(j) ANDA applicants as to which listed drugs are the RLDs (versus the reference standards) for a drug product. For some drug products, however, these changes revealed that no product is identified as being approved under an NDA (in either the active or discontinued sections of the Orange Book) that could serve as an RLD for a 505(j) ANDA. The lack of an RLD is confusing because the Orange Book reflects that there are approved ANDAs for the drug product, including ANDAs identified as reference standards. One reason for this lack of an RLD is that some of the products listed in the Orange Book and identified as being approved in an "ANDA" are actually drugs that were approved for safety and effectiveness under section 505(c) of the FD&C Act in PANDAs that appeared to have been identified as RLDs before the 2017 update to the Orange Book. As noted previously, products approved in PANDAs could be unique products that differed from products approved under pre-1962 NDAs in various ways, including in their active ingredient, route of administration, dosage form, or strength. In addition, even when certain listed drugs approved in a PANDA appear to be pharmaceutical equivalents (as defined in § 314.3(b)) of products approved under an NDA, these products can differ from the products approved under the NDA in other respects, including in the approved conditions of use reflected in the labeling or in their formulation, and may not have been determined to be bioequivalent to the products approved under an NDA. Further, even if the drug product approved in a PANDA was a duplicate of a drug product that was at one time also approved and marketed under an NDA, if the product approved under the NDA was no longer marketed when the Orange Book was first published in October 1980, it was not listed in the Orange Book.

D. Designation of Additional Drugs as RLDs

In light of the changes to the Orange Book in 2017, FDA examined the types of products for which there were no RLDs designated and determined that many were approved in PANDAs.

After consideration of the history of PANDAs, FDA determined that it was appropriate and consistent with FDA's general practice regarding the designation of RLDs to designate PANDA products as RLDs because these products were approved for safety and effectiveness under section 505(c) of the FD&C Act. In addition, as noted in section I.C, many of these products appeared to have been identified as RLDs before the 2017 update to the Orange Book. Designation of the PANDA products as RLDs provides clarity both to prospective 505(j) ANDA applicants seeking to make generic versions of these products, and to applicants of 505(b)(2) applications that there is a finding of safety and effectiveness for these products that may be relied upon for approval. In addition, it is aligned with FDA's efforts to help advance competition and increase patient access to more affordable medicines.

FDA has begun adding RLD designations for PANDAs to the Orange Book and will continue making these designations as expeditiously as resources permit. If a prospective 505(j) ANDA applicant is seeking to duplicate a product approved in a PANDA that has not yet been designated as an RLD by FDA, the prospective applicant may submit controlled correspondence to FDA identifying the drug it intends to duplicate and asking FDA to designate that drug as an RLD (see FDA's guidance for industry, "Controlled Correspondence Related to Generic Drug Development," announced in 85 FR 81928 (December 17, 2020)).[7]

To aid stakeholders in identifying PANDAs, FDA has posted a list of the products currently included in the Orange Book and identified as an "ANDA" in the Orange Book that were approved in a PANDA for safety and effectiveness under section 505(c) prior to the enactment of the Hatch-Waxman Amendments. This list includes only PANDAs described in this notice, i.e., those abbreviated applications submitted under section 505(b) of the FD&C Act and does not include applications for antibiotic drug products approved under section 507 of the FD&C Act before the enactment of the Food and Drug Administration Modernization Act of

[7] For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/regulatory-information/search-fda-guidance-documents.

1997 (FDAMA). This list is available under "Additional Resources" on FDA's "Approved Drug Products with Therapeutic Equivalence Evaluations (Orange Book)" web page (available at https://www.fda.gov/drugs/drug-approvals-and-databases/approved-drug-products-therapeutic-equivalence-evaluations-orange-book). In addition, the Orange Book provides information about the approval date of listed drugs,[8] allowing interested persons to refer to this information to determine which products identified as being approved in an ANDA in the Orange Book were approved before the enactment of the Hatch-Waxman Amendments.[9]

II. Additional Issues for Consideration and Request for Comments

The Agency is seeking input from holders of PANDAs and other interested stakeholders on several issues related to FDA's post-approval regulation of drug products approved in PANDAs. As explained in section I of this notice, PANDAs were submitted under section 505(b) and approved under section 505(c) of the FD&C Act, which are the same provisions under which NDAs are submitted and approved. However, PANDA products have historically been overseen by FDA's Office of Generic Drugs and are included in the definition of *abbreviated new drug application* for user fee purposes under the Generic Drug User Fee Amendments (GDUFA)[10], which specify that this term includes an abbreviated new drug

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[8] For products approved prior to January 1, 1982, the electronic version of the Orange Book indicates the product was "Approved Prior to Jan. 1, 1982" under Product Details in the Approval Date field, and the printed version of the Orange Book has a blank Approval Date field. For products approved on or after January 1, 1982, the electronic and printed versions of the Orange Book provide the specific date of approval in the Approval Date field.

[9] The Hatch-Waxman Amendments were signed into law on September 24, 1984. PANDAs that were submitted before September 24, 1984, were processed by FDA in accordance with the procedures that existed before the passage of the Hatch-Waxman Amendments. See November 16, 1984, letter to interested persons from Harry M. Meyer, Jr., M.D., Director, FDA's Center for Drugs and Biologics. The list of PANDAs posted on FDA's Orange Book web page (https://www.fda.gov/drugs/drug-approvals-and-databases/approved-drug-products-therapeutic-equivalence-evaluations-orange-book) includes all the abbreviated applications approved on or before September 24, 1984. FDA is aware that certain applications submitted before this date but approved after this date and identified as ANDAs in the Orange Book were approved under section 505(c) of the FD&C Act; FDA will update this list as appropriate to include such applications. If a prospective 505(j) ANDA applicant is seeking to duplicate a product approved after September 24, 1984, and the applicant believes the application for the product was submitted before that date and approved under section 505(c) of the FD&C Act, the prospective applicant may submit controlled correspondence to FDA identifying the drug they intend to duplicate and asking FDA to designate that drug as an RLD. The controlled correspondence should include any information known to the prospective applicant that supports the belief that the identified drug was approved in a PANDA. When FDA receives such designation requests, it will evaluate whether the product was approved under section 505(c) of the FD&C Act in determining whether to grant the request.

[10] See Title III of the Food and Drug Administration Safety and Innovation Act (Pub. L. 112-144) and Title III of the FDA Reauthorization Act of 2017 (Pub. L. 115-52).

application submitted pursuant to regulations in effect prior to the implementation of the Drug Price Competition and Patent Term Restoration Act of 1984 (see 21 U.S.C. 379j–41). PANDAs are not included in the FD&C Act statutory definition of the term *abbreviated drug application*, which is limited to applications submitted under section 505(j) of the FD&C Act (see 21 U.S.C. 321(aa)).

FDA recognizes that PANDAs may have been treated similarly to 505(j) ANDAs in some respects over the decades after the enactment of the Hatch-Waxman Amendments, and that there may be confusion among holders of PANDAs about the applicability of certain statutory and regulatory provisions to their products and in particular, whether their products are subject to the requirements that apply to other 505(b) applications or to those that apply to 505(j) applications (to the extent there are differences between the two), including with respect to requirements regarding labeling updates, patent listing, eligibility for exclusivity, and certain drug safety-related requirements or procedures.

For example, with respect to labeling updates, FDA is aware that some PANDA holders have followed procedures applicable to 505(b) applications when proposing labeling updates for their products (e.g., submitting labeling supplements and making labeling changes independent of the pre-1962 NDA product or products that were listed in the DESI notice). However, FDA is also aware that some PANDA holders have followed procedures applicable to 505(j) ANDA holders when proposing labeling updates for their products (e.g., submitting labeling supplements to conform to labeling changes approved for a pre-1962 NDA product listed in a relevant DESI notice).

With respect to patent listing, to FDA's knowledge, PANDA holders have neither sought to list patent information in the Orange Book for their products after the enactment of the Hatch-Waxman Amendments, nor have they submitted patent listing information when submitting supplements to their approved applications during the years after the enactment of the Hatch-Waxman Amendments. Similarly, PANDA holders have generally not submitted supplements

containing reports of new clinical investigations or sought exclusivity under provisions applicable to 505(b) applications (see, e.g., section 505(c)(3)(E)(iv) and 505(j)(5)(F)(iv) of the FD&C Act) following enactment of the Hatch-Waxman Amendments.

FDA is also aware that there may be confusion among PANDA holders about the applicability of certain safety-related requirements to their applications. For example, section 505(o) of the FD&C Act, which relates to postmarket studies and clinical trials and labeling, and section 505-1 of the FD&C Act, which relates to risk evaluation and mitigation strategies, reflect some differences in the safety-related requirements or procedures that apply to 505(b) application holders versus 505(j) ANDA holders, and PANDA holders may consider the requirements that apply to 505(j) ANDA holders to also apply to their applications.

Although, as noted in section I of this notice, PANDAs are section 505(b) applications, FDA understands, as outlined above, that the holders of some PANDAs may have been following various requirements applicable to 505(j) ANDAs over the years after the enactment of the Hatch-Waxman Amendments, and that for them to instead follow requirements applicable to 505(b) applications could be a change in practice. FDA also understands that PANDAs are a unique category of 505(b) applications and that there could be valid reasons to treat PANDAs differently from other 505(b) applications in certain circumstances, to the extent permitted by the applicable statutory provisions.

FDA is seeking input from PANDA holders and other interested stakeholders on whether there are regulatory or policy reasons for treating PANDAs differently from other 505(b) applications, consistent with the statutory requirements for applications submitted under section 505(b) and approved under section 505(c) of the FD&C Act. To facilitate this input, FDA has developed the following list of questions. These questions are not meant to be exhaustive, and FDA is also interested in any other pertinent information stakeholders would like to share on this topic. In all cases, FDA encourages stakeholders to provide the specific rationale and basis for their comments, including any available supporting data and information.

Questions

1. Given the legal requirements in place for applications submitted under section 505(b) and approved under section 505(c) of the FD&C Act, are there regulatory or policy rationales for treating PANDAs differently from other 505(b) applications in certain respects, in particular with respect to the following:
    1.1. Labeling requirements, including requirements related to updating product labeling to reflect certain types of newly acquired safety-related information by submitting a "changes being effected" (CBE-0) supplement to FDA?
    1.2. Patent listing requirements?
    1.3. Eligibility for exclusivity?
    1.4. Certain safety-related requirements, such as the postmarket studies and clinical trials or safety-labeling change requirements in section 505(o) of the FD&C Act or the risk evaluation and mitigation strategies requirements in section 505-1 of the FD&C Act?

    In responding to the questions above, please provide a specific rationale for treating these applications differently.
2. To the extent that PANDA holders are expected to make changes to their current practices, what factors should FDA consider in determining a reasonable amount of time for PANDA holders to make such changes to their practices?
3. Are there additional steps FDA should take to highlight for PANDA holders that their "abbreviated new drug application" is a PANDA, i.e., that it is a 505(b) application?
4. Are there additional steps FDA should take beyond posting the list on the Orange Book website to aid other interested persons in identifying PANDAs?
5. Are modifications needed to the list of PANDAs posted on the Orange Book website for accuracy? For example, are some PANDAs missing from the list?

6. Are there other issues FDA should consider in assessing the regulatory framework for PANDAs under the FD&C Act? Please provide specific examples and explain FDA's authority to address these issues.

Dated: August 10, 2021.

Lauren K. Roth,

Acting Principal Associate Commissioner for Policy.

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